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Review

Epigenetic changes of DNA repair genes in cancer

Christoph Lahtz and Gerd P. Pfeifer*

Department of Cancer Biology, Beckman Research Institute, City of Hope, Duarte, CA 91010, USA
* Correspondence to: Gerd P. Pfeifer, E-mail: gpfeifer@coh.org

'Every Hour Hurts, The Last One Kills'. That is an old saying about getting old. Every day, thousands of DNA damaging events take place in each cell of our body, but efficient DNA repair systems have evolved to prevent that. However, our DNA repair system and that of most other organisms are not as perfect as that of *Deinococcus radiodurans*, for example, which is able to repair massive amounts of DNA damage at one time. In many instances, accumulation of DNA damage has been linked to cancer, and genetic deficiencies in specific DNA repair genes are associated with tumor-prone phenotypes. In addition to mutations, which can be either inherited or somatically acquired, epigenetic silencing of DNA repair genes may promote tumorigenesis. This review will summarize current knowledge of the epigenetic inactivation of different DNA repair components in human cancer.

Keywords: DNA methylation, DNA repair, epigenetics

Introduction

Cancer is characterized by uncontrolled malignant growth and cell division. Cancer cells have a higher proliferation rate than their corresponding normal tissue and they often have lost the ability to undergo programmed cell death (apoptosis). Furthermore, they can acquire the capability to separate from their original tissue and can develop metastasis in other regions of the body. Major causes of disordered cellular programming in cancer are genetic and epigenetic changes. For example, point mutations, deletions, duplications, insertions, translocations, chromosome aberrations, viral infections, and epigenetic inactivation represent various types of potentially cancer-causing events. These mechanisms may affect the DNA sequence and/or may change the function and regulation of the gene products or lead to a loss of function.

A special subset of cancer-relevant genes is represented by deregulated tumor suppressor genes and oncogenes. Genetically changed or over-expressed protooncogenes (oncogenes) promote aberrant cell growth and the products of tumor suppressor genes commonly control cell division and genetic stability. Tumor suppressor genes controlling cell growth are critical, but their importance is probably equal to that of genes involved in DNA repair systems. Effective DNA repair is at the backbone of cancer-free survival. Mutations in DNA repair genes of the nucleotide excision repair (NER) group (XP genes in xeroderma pigmentosum patients), mutations affecting the mismatch repair (MMR) genes [in patients with inherited colorectal cancer (CRC) predisposition], DNA crosslink repair (Fanconi anemia genes), and several others are the cause of inherited cancer syndromes. As an alternative mechanism to genetic mutation, a DNA repair system may be inactivated or decreased in effectiveness by epigenetic gene inactivation mechanisms affecting DNA repair genes. In this review, we will discuss some examples of such mechanisms in specific human cancers (summarized in Table 1).

Epigenetic mechanisms in gene regulation

Epigenetic mechanisms are used in many different ways for control of gene expression. Epigenetic changes never involve a change in the primary DNA sequence or a change in base pairing but are reflected primarily in DNA cytosine modification patterns, histone post-translational modifications, or deposition of certain histone variants along specific gene sequences. These epigenetic modifications of genes are generally reversible, but can get transmitted to the daughter cells (Laird, 2005). For example, one type of epigenetic change that can occur is that the chromatin structure changes from an open active configuration, also referred to as euchromatin, to a densely packed inactive chromatin structure, the so-called heterochromatin.

One common and perhaps the most permanent and stable mechanism of epigenetic gene inactivation is the methylation of the 5-carbon of the DNA base cytosine in the 5′-CpG-3′ dinucleotide sequence context of CpG island or promoter regions. These methylation reactions carried out by DNA cytosine methyltransferases are a main component of epigenetic regulatory mechanisms in mammals (Baylin et al., 2001). In tumor tissues, tumor suppressor genes are often inactivated epigenetically by methylation when compared with normal tissue. The DNA methylation events are often preceded by changes in chromatin structure and histone modifications, for example, by loss of the active histone mark H3K4 trimethylation (Figure 1). Sequences that

Table 1 Methylated DNA repair genes in cancer.

Repair system	Genes	Known cancer types
Base excision repair (BER)	MBD4	Colorectal cancer (cell lines), ovarian cancer (cell lines) (Howard et al., 2009), multiple myeloma (cell lines) (Peng et al., 2006)
	TDG	Multiple myeloma (cell lines) (Peng et al., 2006)
	OGG1	Thyroid cancer (cell lines and tumors) (Guan et al., 2008)
Direct reversal of DNA damage	MGMT	Colon cancer (Herfarth et al., 1999), gastric carcinoma (Oue et al., 2001), glioblastoma (Esteller et al., 2000), head and neck squamous cell carcinoma (cell lines) (Goldenberg et al., 2004), non-small cell lung cancer (Wolf et al., 2001)
Nucleotide excision repair (NER)	XPC	Bladder cancer (Yang et al., 2010)
	RAD23A	Multiple myeloma (cell lines) (Peng et al., 2005)
	ERCC1	Glioma (cell lines and tumors) (Chen et al., 2010)
Mismatch excision repair (MMR)	MLH1	Acute myeloid leukemia (Seedhouse et al., 2003), gastric cancer (Fleisher et al., 1999), neck squamous cell carcinoma (Liu et al., 2002), non-small cell lung cancer (Wang et al., 2003), oral squamous cell carcinoma (Czerninski et al., 2009), ovarian cancer (Gras et al., 2001a), sporadic colorectal cancer (Kane et al., 1997), sporadic endometrial carcinoma (Esteller et al., 1998)
	MSH2	Colorectal cancer (Lawes et al., 2005), non-small cell lung cancer (Wang et al., 2003), oral squamous cell carcinoma (Czerninski et al., 2009), ovarian cancer (Zhang et al., 2008)
	MSH3	Gastric carcinoma (in elderly) (Kim et al., 2010), sporadic colorectal cancer (Benachenhou et al., 1998)
	MSH6	Colorectal cancer (Lawes et al., 2005)
Homologous recombination	BRCA1	Breast cancer (Dobrovic and Simpfendorfer, 1997), ovarian cancer (Catteau et al., 1999), gastric cancer (Bernal et al., 2008), non-small cell lung cancer (Lee et al., 2007), uterine cancer (Xing et al., 2009), bladder cancer (Yu et al., 2007)
Non-homologous end-joining	XRCC5	Non-small cell lung cancer (Lee et al., 2007)
Editing and processing nucleases	FEN1	Breast cancer (hypomethylated) (Singh et al., 2008)
Genes defective in diseases associated with sensitivity to DNA damaging agents	WRN	Breast cancer (cell lines and tumors), colon cancer (cell lines), colorectal cancer, gastric cancer, leukemia (cell lines), non-small cell lung cancer, prostate cancer, thyroid cancer (Agrelo et al., 2006)
	ATM	Breast tumors (not confirmed) (Vo et al., 2004; Treilleux et al., 2007; Flanagan et al., 2009), colorectal cancer (cell lines) (Kim et al., 2002), head and neck squamous cell carcinoma (Ai et al., 2004)
Fanconi anemia	FANCC	Sporadic leukemia (0.7–3.1%) (Hess et al., 2008)
	FANCF	Cervical cancer (Narayan et al., 2004), head and neck squamous cell carcinoma, non-small cell lung cancer (Marsit et al., 2004), ovarian cancer (cell lines and tumors) (Olopade and Wei, 2003)
	FANCL	Sporadic leukemia (~1%) (Hess et al., 2008)
Other conserved DNA damage response genes	CHK2	Glioma (Wang et al., 2010), non-small cell lung carcinoma (cell lines and tumors) (Kim et al., 2009)

have undergone DNA methylation often harbor repressive histone modifications such as H3K9 trimethylation.

Epigenetic inactivation of DNA repair genes

Two major types of DNA repair exist. The first one repairs DNA damage that arises from external sources such as UV light or ionizing rays and from endogenous DNA damage, for example, due to oxidative stress. To this type of repair belong the base excision repair (BER) pathway, the direct reversal of DNA damage, and the NER pathways. The other general mechanism of repair deals with the mistakes made during DNA replication. This system includes factors involved in MMR, homologous recombination, certain DNA helicases, editing and processing nucleases, and other genes, which are defective in diseases associated with sensitivity to DNA damaging agents (Jackson and Bartek, 2009; Ciccia and Elledge, 2010).

Base excision repair

In BER, generally a single damaged DNA base is removed by a DNA glycosylase-type enzyme. The resulting abasic site is then repaired by additional steps including DNA backbone incision, gap filling, and ligation. The most common mutation found in human genetic diseases and cancer is the C to T transition

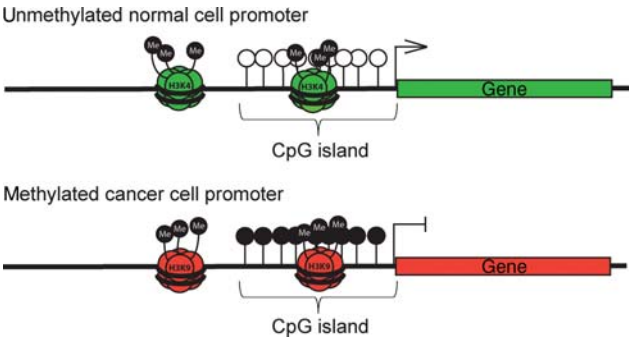

Figure 1 Epigenetic inactivation of a DNA repair gene promoter. Promoters are often embedded within CpG islands. These CpG-rich sequences are usually unmethylated in normal tissues and are associated with the active histone mark H3K4me3. H3K4me3 prevents DNA methylation. During tumorigenesis, the CpG island becomes methylated, is associated with inactive chromatin marks (e.g. H3K9me3), and the gene becomes silenced.

mutation found at CpG dinucleotides. These mutations are thought to arise from deamination of 5-methylcytosine (Pfeifer, 2006). The methyl-CpG binding domain protein 4 (MBD4; also known as MED1) has the ability to bind methylated DNA (Hendrich and Bird, 1998), and furthermore, it preferentially binds to the T:G mismatches at CpG sites (Hendrich et al., 1999). These mismatches are the product of deamination of methylated CpGs. MBD4 has a glycosylase domain and is able

to repair these mismatches by removing thymine from DNA (Hendrich et al., 1999). MBD4 has the same function as the thymine DNA glycosylase (TDG) protein (Wiebauer and Jiricny, 1989; Yoon et al., 2003). Thus, MBD4 and TDG belong to a group of BER enzymes likely to be important for counteracting a process of endogenous DNA damage, hydrolytic deamination of 5-methylcytosine. For these two DNA repair genes, *MBD4* and *TDG*, promoter methylation has been found in different cancer types. Several multiple myeloma cell lines (KAS-6/1, KMS-11, OPM2, KMS-12, and JIM3) showed promoter methylation and decreased gene expression compared with normal plasma cells for *TDG* (Peng et al., 2006). *MBD4* is significantly methylated in CRC cell lines and ovarian cancer (OC) cell lines (Howard et al., 2009). In sporadic CRC, promoter methylation of *MBD4* is an early event in tumorigenesis and could be used as a prognostic factor.

Another BER gene for which promoter methylation has been found is *OGG1*. *OGG1* repairs oxidatively damaged guanine bases in DNA and mutations of this gene may be involved in tumorigenesis (Arai et al., 1997; Chevillard et al., 1998; Shinmura and Yokota, 2001). But at this point, a methylated promoter of *OGG1* is only known in 5% of thyroid cancer and in some thyroid cancer cell lines (Guan et al., 2008).

Direct reversal of DNA damage

MGMT encodes the O^6-methylguanine-DNA methyltransferase (Tano et al., 1990; Natarajan et al., 1992). This enzyme repairs DNA alkylation damage. Alkylation reactions lead to formation of a methyl group (CH_3-) at the O^6 position of guanine. O^6-methylguanine pairs with thymine rather than cytosine and promotes G:C to A:T mutations. MGMT repairs this damage and protects the DNA by transferring the methyl group to a cysteine residue in the protein. Epigenetic inactivation by promoter methylation of the *MGMT* gene is very well established. This gene is epigenetically silenced in a variety of cancers (Esteller et al., 1999). Specifically, *MGMT* methylation is found in glioblastomas (Esteller et al., 2000; Mellai et al., 2009; Shamsara et al., 2009), colon cancer (Herfarth et al., 1999; Ogino et al., 2007), non-small cell lung cancer (NSCLC) (Wolf et al., 2001; Wu et al., 2008), gastric carcinoma (Oue et al., 2001), head and neck squamous cell carcinoma (HNSCC) (Goldenberg et al., 2004; Maruya et al., 2004; Steinmann et al., 2009), and many other cancer types. Interesting is the fact that glioma patients with a methylated and inactivated *MGMT* gene who were treated by chemotherapy with alkylating agents, such as temozolomide, have a better survival relative to patients with an unmethylated and active *MGMT* gene (Esteller et al., 2000; Hegi et al., 2005; Kaina et al., 2007).

Nucleotide excision repair

The NER system consists of two sub-pathways. The global genome repair (GGR) mechanism repairs DNA damage in transcriptionally inactive parts of the genome (Sugasawa et al., 2001; Riedl et al., 2003). The second NER component is responsible for repair of transcribed DNA and is referred to as transcription-coupled repair (TCR) (Fousteri and Mullenders, 2008; Hanawalt and Spivak, 2008). These two NER functions differ in the damage recognition step. The protein encoded by the xeroderma pigmentosum group C (XPC) gene is a subunit of these damage recognition complexes and is essential for GGR (Friedberg, 2001; Riedl et al., 2003). For the TCR pathway, recognition of the DNA damage-blocked RNA polymerase by transcription-repair coupling factors is important. After damage recognition, the GGR and TCR have the same or similar subsequent steps involved in nucleotide excision and gap filling.

Using a luciferase assay, Wu et al. (2007) found that the promoter region −175 to −1 upstream of the *XPC* gene is important for the regulation of this gene. Furthermore, they found that in different cell lines (Calu-1, H1355, and H441), this region is highly methylated and methylation regulates the expression level of *XPC*. The first example for a primary tumor characterized by *XPC* gene methylation was bladder cancer (methylation level of 32.4% in bladder cancer versus 6.1% in normal tissue) (Yang et al., 2010). In addition, it is known that two other genes, which are part of the NER system, are methylated in human tumors. The genes *RAD23A* and *ERCC1*, which are involved in DNA damage recognition and incision, respectively, are also inactivated through promoter methylation. The *RAD23A* gene is methylated in the multiple myeloma cell line KAS 6/1 (Peng et al., 2005) and *ERCC1* is methylation-silenced in glioma cell lines and glioma tumors (Chen et al., 2010).

Mismatch excision repair

The DNA MMR protein MLH1 is encoded by the MutL homolog 1 (MLH1) gene in humans and is a homologue of the DNA MMR gene *mutL* of *Escherichia coli*. The MMR function is associated with DNA replication, to correct for deficiencies in DNA polymerase proofreading function. A missing gene or mutations of this gene and other MMR genes (*MSH2*, *MSH6*, or *PMS2*) leads to microsatellite instability (MSI) and this dysfunction is highly associated with hereditary non-polyposis colon cancer (HNPCC or Lynch syndrome) (Bronner et al., 1994).

It has been shown that methylation in the promoter region of *MLH1* correlates with decreased activity of the gene (Kane et al., 1997). Next to the main cancer type where this gene is inactivated, HNPCC, this gene is epigenetically inactivated also in other types of cancer, for example, in sporadic endometrial carcinoma (Esteller et al., 1998), gastric cancers (Fleisher et al., 1999), sporadic CRC (Kane et al., 1997; Herman et al., 1998), ovarian tumors (Gras et al., 2001a), NSCLC (Wang et al., 2003), oral squamous cell carcinoma (SCC) (Czerninski et al., 2009), neck SCC (Liu et al., 2002; Steinmann et al., 2009), and acute myeloid leukemia (AML) (Seedhouse et al., 2003). Constitutional methylation of the *MLH1* gene, characterized by soma-wide methylation of a single allele and transcriptional silencing, has been identified in a subset of Lynch syndrome cases lacking a sequence mutation in *MLH1* (Gazzoli et al., 2002; Suter et al., 2004; Hitchins et al., 2007). This particular example provides strong support for the proposal that methylation of a DNA repair gene can be a crucial mechanism in carcinogenesis.

Several other genes belong to the MMR system. The activity of the genes coding for MutS homologues 2, 3, and 6 (*MSH2*, *MSH3*, and *MSH6*) is also controlled by promoter methylation. The

function of these gene products is in mismatch recognition. *MSH2*, for example, is methylated in CRC (Lawes et al., 2005; Nagasaka et al., 2010), primary NSCLC (Wang et al., 2003), oral SCC (Czerninski et al., 2009), and OC (Zhang et al., 2008). *MSH2* is also highly methylated in neurofibromatosis type 1 (Titze et al., 2010). Further, it has been found that methylation occurs in CRC in the promoter region of *MSH6* (Lawes et al., 2005). For *MSH3*, it was found that it is epigenetically inactivated in sporadic CRC (Benachenhou et al., 1998). In elderly gastric carcinoma patients, *MSH3* was significantly more methylated than in younger patients (Kim et al., 2010). In conclusion, methylation of the gene *MLH1* may have considerable importance in cancer development and as a prognostic factor and the genes *MSH2*, *MSH3*, and *MSH6* are interesting candidates as well.

Homologous recombination

If it is not possible to repair the DNA damage before replication, the DNA may be repaired by homologous pairing. Because of DNA polymerase-blocking damage, DNA strand breaks will be generated, which can be repaired by the homologous recombination repair system. The BRCA1 and BRCA2 (Breast Cancer 1 and 2) proteins are involved in this repair pathway. The *BRCA1* and *BRCA2* genes are tumor suppressor genes and the proteins, together with RAD51, form a complex to repair DNA strand breaks (Duncan et al., 1998; Yoshida and Miki, 2004). These genes are characterized by tumor-specific mutations in inherited breast and OC (Miki et al., 1994; Wooster et al., 1994; Narod, 2010). A few years after their initial discovery, researchers found promoter methylation for *BRCA1* which correlated with low mRNA levels (Dobrovic and Simpfendorfer, 1997). For *BRCA2*, it has been found that a low mRNA level is generally not caused by hypermethylation of the promoter (Gras et al., 2001b; Hilton et al., 2002). *BRCA1* is most often methylated in breast and OC but also in gastric cancer (Bernal et al., 2008), NSCLC (Lee et al., 2007), uterine cancer (Xing et al., 2009), and bladder cancer (Yu et al., 2007).

Non homologous end-joining

The gene product of *XRCC5* is the protein K80 (Taccioli et al., 1994). Together with the gene product of *XRCC6*, it forms the 80 and 70 kDa subunits of the K70/K80 heterodimer protein Ku, which is involved in the binding of double-strand breaks (DSBs) during non-homologous end-joining (Difilippantonio et al., 2000; Koike, 2002). Together with the DNA-PKcs (DNA-dependent protein kinase catalytic subunit), the Ku heterodimer forms the full complex DNA-PK (Carter et al., 1990). At this time, an epigenetic inactivation of this pathway of DNA repair is only known for the gene *XRCC5* (Lee et al., 2007). The authors showed that 21% of all NSCLCs were methylated in the promoter region of *XRCC5*. Furthermore, 15% of adenocarcinomas and 32% of SCCs were methylated and had a low protein expression level (Lee et al., 2007). This area of research should be extended into other types of cancer to see whether *XRCC5* or other genes of this pathway may play an important role as targets of epigenetic silencing.

Editing and processing nucleases

FEN1 codes for the flap structure-specific endonuclease 1 (also known as DNase IV) and is a 5′-nuclease (Hiraoka et al., 1995). This protein is important for the processing of the 5′ ends of Okazaki fragments during lagging strand DNA synthesis (Henneke et al., 2003) and removes the 5′ flaps during long-patch BER (Klungland and Lindahl, 1997). FEN1 may be involved in the repair of DNA DSBs by non-homologous end-joining (Wu et al., 1999) and homologous recombination (Kikuchi et al., 2005). Furthermore, it is important for genomic stability (Singh et al., 2007).

FEN1 is highly expressed in proliferative tissues such as bone marrow, testes, and thymus (Otto et al., 2001) and is overexpressed in testis, lung, and brain tumors (Nikolova et al., 2009) and in prostate cancer (Lam et al., 2006), metastatic prostate cancer cells (LaTulippe et al., 2002), neuroblastomas (Krause et al., 2005), and pancreatic cancer (Iacobuzio-Donahue et al., 2003). *FEN1* expression is also increased in lung cancer cell lines (SCLC and NSCLC) (Sato et al., 2003) and gastric cancer cell lines (Kim et al., 2005).

These data indicate that an increased expression level of *FEN1* leads to cancer or is associated with cancer. It has been shown that not epigenetic inactivation but rather an absence of methylation (DNA hypomethylation) of *FEN1* is associated with breast cancer (Singh et al., 2008). Compared with normal tissue with a 57.6% methylation level, the methylation level in breast tumors was only 1.2% (Singh et al., 2008). Because of the many cancer types, where *FEN1* expression is increased, this finding gives a useful hint to look for additional epigenetic changes affecting this gene in other cancer types.

Genes defective in diseases associated with sensitivity to DNA-damaging agents

Werner syndrome is an autosomal recessive disorder. It is characterized by accelerated aging of the mesodermal tissue. The responsible gene (*WRN*) is a DNA helicase and a RecQ family member (Gray et al., 1997). The *WRN* gene is methylated in a large number of different cancer types. Examples are cell lines from colon cancer, breast cancer, and leukemia, and it is most highly methylated in primary tumor samples of CRC (37.9%), NSCLC (37.5%), gastric cancer (25%), prostate (20%), breast (17.2%), and thyroid (12.5%) (Agrelo et al., 2006; Kawasaki et al., 2008).

The product of the *Ataxia telangiectasia mutated* (*ATM*) gene is a serine protein kinase and tumor suppressor. When a DNA DSB has been generated, cell cycle arrest is initiated by the ATM signaling network. After an initial finding that CRC cell lines are methylated at the *ATM* gene (Kim et al., 2002), it has been found that also primary breast tumors are very often methylated (78%) (Vo et al., 2004). But these high methylation frequencies do not seem to be a general finding in breast cancer. One group could not confirm these results (Treilleux et al., 2007). Another group could show that *ATM* is methylated in blood

samples of breast cancer patients (Flanagan et al., 2009). Therefore, the relevance of *ATM* gene methylation in breast cancer is not clear. Furthermore, *ATM* is significantly methylated (25%) in HNSCCs (Ai et al., 2004).

Fanconi anemia

Fanconi anemia is an autosomal recessive genetic disorder. Thirteen genes are associated with this disease. These genes are DNA repair genes and mutation of each of them leads to the same disorder. The genes are called Fanconi anemia, complementation group A, B, C, D1, D2, E, F, G, I, J, L, M, and N (*FANCA-N*). Assembly of a complex of FANC proteins is activated by replicative stress, particularly DNA damage caused by cross-linking agents. At this time, epigenetic inactivation is only known for a few of these genes. Methylation of *FANCF* is mostly observed in primary OC and cell lines (Olopade and Wei, 2003). The range of promoter methylation was between 21% (Olopade and Wei, 2003) and 24% (Dhillon et al., 2004) and up to 27.8% (Wang et al., 2006) in primary tumors. One result showed only 13.2% methylation frequency (Lim et al., 2008). Furthermore, promoter methylation was found in NSCLC with 14% and in HNSCC with 15% (Marsit et al., 2004). A high methylation rate of *FANCF* was also found in cervical cancer with 30% (Narayan et al., 2004). In contrast to these findings, no or just very rare promoter methylation was found in breast cancer (Wei et al., 2008; Tokunaga et al., 2009). Additionally, very minimal promoter methylation was found in the genes *FANCC* and *FANCL* in sporadic acute leukemia. AML showed a 0.7% methylation frequency for *FANCC*; in acute lymphoblastic leukemia (ALL), the methylation frequency was 3.1% for *FANCC* and the gene *FANCL* was methylated in 1% of ALL cases (Hess et al., 2008). In general, not much is known about epigenetic inactivation of this whole gene family in cancer.

Other conserved DNA damage response genes

The last interesting candidate is the CHK2 checkpoint homologue (CHK2). CHK2 is a protein kinase functioning in an important DNA damage response pathway and is involved in regulation of cell cycle arrest (Matsuoka et al., 1998). It has been shown that this gene is inactivated by promoter methylation in NSCLC with 28.1% tumor methylation frequency in total (squamous cell lung carcinoma 40%; adenocarcinoma 19%) (Kim et al., 2009) and in NSCLC cell lines (Zhang et al., 2004). In gliomas, *CHK2* is methylated in the proximal CpG island promoter and is significantly down-regulated (Wang et al., 2010). For breast cancer, colon cancer, and OC, it has been shown that methylation in the proximal CpG island in tumors as well as in normal tissue has no influence on cancer progression (Williams et al., 2006). The distal CpG island is unmethylated in these cancer types (Williams et al., 2006). Additionally, no methylation in breast cancer was found (Sullivan et al., 2002). In conclusion, this gene shows some interesting findings and it may be worth to look for *CHK2* methylation in other cancer types.

Conclusions

Epigenetic inactivation of DNA repair genes in cancer has been reported for several DNA repair pathways including BER, NER, DNA MMR, and several other DNA damage processing mechanisms. Within one DNA repair pathway, specific genes are often preferentially methylated. It remains to be determined whether this specificity is due to selection of particular repair gene silencing events in promoting tumorigenesis or is due to preferential targeting of the DNA methylation machinery to specific DNA repair gene promoters.

It can be assumed that these epigenetic inactivation processes can result in an increase in genetic instability during tumorigenesis that can be directly attributed to the deficiencies in DNA repair. Therefore, inactivation of DNA repair genes can be seen as an important event in cancer initiation and/or progression by reducing genomic stability leading to genetic aberrations at other important gene loci. Such a mechanism is proven for inactivation of MMR pathways in colorectal tumors but awaits direct confirmation for a number of other DNA repair genes that are found methylated in tumors. On the other hand, diminished DNA repair is expected to lead to reduced cell survival in general, and additional events are likely occurring that enable a cell with reduced repair capacity to undergo uncontrolled proliferation instead of cell death (e.g. mutation in *TP53*). Interestingly, reduced repair capacity for alkylated guanines by promoter methylation of the *MGMT* gene has provided a therapeutic benefit in patients with glioma (Esteller et al., 2000). Conversely, inactivation of the MMR system has been associated with resistance of cells to cisplatinum treatment (Fink et al., 1997). With ever-increasing knowledge of the epigenome of specific cancer types, there is now the opportunity to develop chemotherapy regimens tailored to a patient's DNA repair gene status by incorporating information on epigenetic silencing of the relevant genes in the tumor.

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